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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/441,411 | Applicant(s) Scholler ET AL. | |
|---|---|---|---|
| | Examiner David Nikodem | Art Unit 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

## DETAILED ACTION

### *Drawings*

1. New formal drawings are required in this application because groups 4 and 5 in Figure 3 have been denoted using the same symbol. It is impossible to interpret the figure since Groups 4 and 5 are indistinguishable. Applicant is advised to submit a corrected drawing with a corrected figure legend.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term vaccine in claims 1-8 is vague and indefinite in view of the remainder of the preamble of the claim. Implicit in the word vaccine is physiological protection against a disease or pathogen upon challenge with said disease or pathogen. It is unclear how "eliciting or enhancing the titer of antibodies specific for a cell surface antigen" relates to the language "vaccine." It is unclear how the "eliciting or enhancing the titer of antibodies specific for a cell surface antigen" is protective since the specification does not teach protection (i.e. tumor growth still occurs

after immunization, albeit to a lesser degree). Furthermore, the specification fails to define the term "vaccine."

4. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The language "enhancing" is vague and indefinite. The specification fails to disclose what the enhancement of antibody titer is relative to; in other words, it is unclear as to what degree of enhancement constitutes enhancement and over what starting level of antibody. Therefore the metes and bounds of this claim language are unclear. A more precise and definite use of the language in the claims is suggested.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for eliciting or enhancing the titer of antibodies for Her2/neu protein, comprising individual expression constructs which each recombinantly express Her2/neu, murine B7.2 or murine 4-1Bb ligand, does not reasonably provide enablement for any vaccine for eliciting or enhancing the titer of antibodies for any cell surface receptor antigen, comprising one or more recombinant expression constructs which express (either as individual expression vectors or as one

expression vector or a combination thereof), any cell surface receptor antigen, and two immune response altering molecules, consisting of any accessory cell agent and any T cell agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

7. The claimed invention is broadly drawn to a vaccine for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising one or more recombinant expression constructs which express (either as individual expression vectors or as one expression vector or a combination thereof) a cell surface receptor antigen, and two immune response altering molecules, consisting of an accessory cell agent and a T cell agent. The claimed invention is further drawn to the expression products of the recombinant expression construct(s) of said vaccine.

8. The specification teaches 1) the construction of four recombinant expression constructs that recombinantly express either rat Neu, murine B7.1, murine B7.2 or murine 4-1Bb ligand, each under the independent control of a CMV promoter (page 50-52) as an independent expression construct, and 2) the immunization of nude mice using combinations of the four recombinant expression constructs (page 53) and demonstrating that the immunization groups (pLNCX-Rat-Neu, pLNCX-Rat-Neu + pLNCX-4-1-Bblig and pLNCX-Rat-Neu + pLNCX-4-1-Bblig + pLNCX-B7.2) had the following: a) an increase in anti-rat Neu antibodies after immunization (Figure 1), b) a greater number of T cells than B cells (Figure 2), with groups 5 and 7 showing

significant increases, and c) partial tumor growth inhibition (Figure 3). The specification further teaches that the immunization of nude mice using a vaccine comprising pLNCX-Rat-Neu + pLNCX-B7.2 resulted in the following a) an increase in anti-rat Neu antibodies after immunization (Figure 1), b) a greater number of T cells than B cells (Figure 2), and c) an increase in tumor size.

9. Claims 1-8 are drawn to vaccines and intended use(s) thereof. The specification provides a general discussion of recombinant expression vector design and construction, as well as a multitude of putative vaccine components (e.g. cell surface receptor antigens and immune response altering molecules) to comprise a vaccine. Although, the specification teaches the construction of the aforementioned recombinant vaccine expression constructs and demonstrates a partial degree of protection with certain vaccines (see paragraph 5 of the instant office action) the specification fails to provide teachings for the construction, delivery and putative effect of any vaccine for eliciting or enhancing the titer of antibodies specific for any cell surface receptor antigen. The specification fails to enable one skilled in the art to use the invention over the full scope as claimed.

10. As a first issue, the specification fails to provide guidance to the skilled artisan on the parameters for vaccine delivery over the breadth of the claimed invention. Eck, *et al.* teaches (page 81) that numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. These include the following: the fate of the DNA vector itself (volume of distribution, rate of clearance into

the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated.

11. The support for a single embodiment of a well known anti-cancer cell surface receptor antigen (i.e. Her2/neu) delivered as a recombinant expression vector in the context of two well known immune response altering molecules (i.e. 4-1Bb ligand and B7.2) into a mouse model prior to tumor formation is insufficient evidence for enablement of any and all vaccines delivering any and all cell surface receptor antigen by any and all routes of delivery with or without a vector encoding and expressing any and all accessory molecules. No general guidelines existed at the time of filing or at present for the synthesis of recombinant expression constructs for the effective delivery of target antigens for vaccination. It would require undue experimentation for one skilled in the art to determine whether or not the vaccine construct could elicit or enhance antibody titers of any or all specific cell surface receptor antigen. Furthermore, it would require undue experimentation for one skilled in the art to determine whether or not any or all immune response altering molecules are co-stimulatory, and furthermore,

with which particular cell surface receptor antigen. Therefore, the invention is not enabled over the full scope as claimed.

12. As a second issue, the specification fails to disclose the effect(s) of the vaccine (combinations of four recombinant expression constructs that express either rat Neu, murine B7.1, murine B7.2 or murine 4-1Bb ligand) in an animal model other than nude mice. The results for vaccine efficacy obtained from vaccination of nude mice can not be extrapolated to humans, since humans are not immunocompromised. It is unpredictable as to whether or not the invention as claimed would provide the intended therapy in humans, and/or an animal model that utilizes non- immunocompromised subjects. It would require undue experimentation for one skilled in the art to determine whether or not the vaccine would elicit or enhance an antibody response in mice other than nude mice. Therefore, the invention is not enabled over the full scope as claimed.

13. As third issue, the specification provides evidence that a group of mice (Group 4) immunized with component vaccine DNA constructs pLNCX-Rat-Neu + pLNCX-B7.2, although having an increase in antibody titer for Neu, did not provide any degree of protection upon disease challenge. Therefore, this combination of vaccine DNA constructs did not function as a vaccine and thus is not enabled because the intended use of a vaccine is not supported by the specification.

14. In claims 1-4 and 7-8, the specification fails to provide teachings of the use of Her2/neu, murine 4-1Bb ligand, and murine B7.2, other than as delivered by individual

expression vectors, whereby a single expression vector expresses a single expression product. It would require undue experimentation for one skilled in the art to synthesis a single expression construct that expresses Her2/neu, murine 4-1Bb ligand, and murine B7.2 whereby an increase in antibody titer is seen. The experimentation required would entail the identification of an expression vector that could functionally express the three said gene products. It is unclear whether or not one vector would be able to express all three gene products at a level seen with the expression of proteins by individual expression constructs. Furthermore, a single expression vector encoding all three gene products would be very large and it is unclear whether the products expressed would be functional (in terms of tertiary structure to determine protein conformation as well as quantity of protein production) to such a level as seen with the individually expressed gene products. Therefore, the invention is not enabled.

### *Claim Rejections - 35 USC § 103*

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoo, Gerstmayer, *et al.*, and Goodwin, *et al.*.

17. The claimed invention has been described in paragraphs 7 and 8 of the instant office action. Hoo teaches (in the claims) a pharmaceutical composition comprising a nucleic acid sequence encoding the tumor-associated antigen Her2/neu. The reference further teaches (page 18) that the pharmaceutical composition of the invention can contain a B7-2 co-stimulatory molecule. The reference further teaches that said tumor associated antigen is expressed by an expression vector construct under the control of a CMV promoter (Fig. 1A). In view of such, the reference teaches the components of the vaccine of the invention as claimed, namely pLNCX-B7.7and pLNCX-Neu.

18. Gerstmayer, *et al.*, teaches (page 4584) that the expression of human B7-2 can function as co-stimulatory molecules and that "the presentation of B7 molecules on the surface of tumor cells *in vivo* might present a promising novel approach for cancer immunotherapy." The reference further teaches (p. 4585) an expression construct that expresses human B7.2. In view of such, the reference teaches the components of the vaccine of the invention as claimed, namely pLNCX-B7.1 and pLNCX-B7.2.

19. Goodwin, *et al.* teaches the molecular cloning and recombinant expression of murine 4-1Bb ligand. Furthermore, the reference teaches that murine 4-1Bb ligand acts a proliferative co-stimulus on activated thymocytes and splenic T cells, resulting in an increased proliferation of activated T cells and thus functions as an immune response altering molecule. The reference further teaches (p. 2638) the expression of murine 4-1Bb ligand by an expression vector construct. In view of such, the reference teaches the component of the vaccine of the invention as claimed, namely pLNCX-4-1-BBlig.

20. The MPEP teaches (section 2144.06) that "[I]t is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In the instant application, the expression constructs enabled by the specification (see paragraph 6 of the instant office action) have all been taught as individual components in the art, as indicated in paragraphs 17-19 of the instant office action. Each of the references teaches the expression and delivery of said gene products with the purpose to stimulate an anti-cancer immune response, *in vivo*. Thus, one of ordinary skill in the art at the time of filing would have been motivated to combine the individual expression constructs known in the art, each expressing Her2/neu, human B7.2 and murine 4-1Bb ligand, respectively, as a vaccine that expresses a combination of the three gene products.

21. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Nikodem whose telephone number is (703) 308-8361. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone

numbers for the organization where this application or proceeding is assigned are (703) 305-3230 for regular communications and (703) 305-3230 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

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April 10, 2000

JOHN L. LeGUYADER
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